Rejection of Claim 36 Under 35 U.S.C. § 101

Claim 36 is rejected under 35 U.S.C. § 101 "because the claimed invention is directed to non-statutory subject matter". It is respectfully submitted that the above rejection does not pertain to the claim as newly amended in that the term "isolated" has been inserted into the claim.

Rejection of Claims 6, 13-23, 26, 37 and 38 Under 35 U.S.C. § 112, Second Paragraph

Claims 6, 13-23, 26, 37 and 38 are rejected under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". It is respectfully submitted that the above rejection does not pertain to the claims as newly amended. The language "small alteration" has been changed in claim 6 and the antecedent basis rejection has been obviated with regard to claims 13-23. Claim 37 also has been changed pursuant to the Examiner's suggestion.

Rejection of Claims 1-38 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 1-38 are rejected under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claims 1-5 of U.S. Patent No. 5,429,923". The Examiner states that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the "instant claims and the claims of '923 are inclusive of methods for diagnosing hypertrophic cardiomyopathy wherein the method comprises detecting the presence or absence of a hypertrophic cardiomyopathy-associated mutation in the RNA of an individual".

It is respectfully submitted that a terminal disclaimer will be filed upon indication of allowable subject matter, if appropriate.

Rejections of Claims 1-31 and 36-38 Under 35 U.S.C. § 102(a)

Claims 1-31 and 36-38 are rejected under 35 U.S.C. §102(a) "as being anticipated by" Rosenzweig et al. (New England Journal of Medicine (1991) 325:1753-1760) and Watkins et al. (New England Journal of Medicine (1992) 326:1108-1114).

The Examiner recognizes that listed inventors of the instant application appear on the cited references but that the Rosenzweig et al. and Watkins et al. references recite additional authors. It is the Examiner's contention that this constitutes invention "by another". It is respectfully submitted that the additional authors that appear on the papers by Rosenzweig et al. and Watkins et al. are not co-inventors of the subject patent application but were either working under the direction and supervision of Dr. Christine Seidman and Dr. Jonathan Seidman or provided materials to them. Therefore, as the references are the result of the work of the Applicants, the articles are not a proper §102(a) reference. The Examiner is respectfully requested to reconsider and withdraw this rejection.

Copies of two declarations under 37 C.F.R. 1.132 by Dr. Jonathan Seidman and Dr. Christine Seidman filed in the parent application of the above-identified application are being submitted concurrently herewith. These declarations essentially state that the additional authors on the Rosenzweig et al. and Watkins et al. references are not co-inventors of the subject matter of the present invention.

Rejection of Claims 24-30 Under U.S.C § 102(b)

Claims 24-30 stand rejected under 35 U.S.C § 102(b) as allegedly being anticipated by Almoguera et al., *Curr. Comm. Mol. Biol.: PCR*, Cold Spring Harbor Laboratory Press, New York (1989) pp. 37-45. This rejection is respectfully traversed.

Almoguera et al. does not anticipate Applicant's invention. Applicants' invention, as defined by amended claim 24, distinguishes over the art by providing a method for identifying hypertrophic cardiomyopathy-associated mutations in a DNA sequence. Almoguera et al. neither discloses the disorder hypertrophic cardiomyopathy nor the nature of mutations, if any, that are associated therewith. Clearly, Almoguera et al. does not disclose a method for identifying hypertrophic cardiomyopathy-associated mutations.

> [A] § 102(b) reference 'must sufficiently describe the claims invention to have placed the public possession of it . . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabline.' . . . The basis for this rule is found in the description requirement of § 102(b).

FMC Corp. v. Manitowoc Co., 2 USPQ2d 1969 (N.D. Ill. 1987) aff'd 5 USPQ2d 112 (Fed. Cir. 1988). Further the absence from a prior art reference of any claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible Inc.*, 230 USPQ 81 (Fed. Cir. 1986).

In view of the above amendments and remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102 is respectfully requested.

Rejection of Claim 36 Under 35 U.S.C § 102(b)

Claim 36 is rejected under 35 U.S.C. § 102(b) "as being anticipated by Eisenberg (Journal Molecular and Cellular Cardiology (March 1991) 23:287-296)". Particularly,

the Examiner states that "Eisenberg teaches RNA probes complementary to the sequences of the B-MHC nucleic acids (see page 289)".

It is respectfully submitted that the above-rejection does not pertain to the claim as newly amended. Newly amended claim 36 is drawn to an isolated RNA probe having ribonucleotides arranged in a sequence which is complementary to at least a portion of ß-cardiac myosin heavy-chain DNA. The probe is claimed as being useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being arranged for use in detecting a hypertrophic cardiomyopathy-associated mutation.

Eisenberg studied the distribution of myosin heavy chain mRNA in normal and hyperthyroid hearts. Eisenberg does not teach or suggest an RNA probe useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being arranged for use in detecting a hypertrophic cardiomyopathy-associated mutation as presently being claimed.

Rejection of Claims 37 and 38 Under 35 U.S.C. § 102(a)

Claims 37 and 38 are rejected under 35 U.S.C. § 102(a) "as being anticipated by Friedman (Basic Research Cardiology (March-April 1992) 87:106-112)". Particularly, the Examiner states that " Friedman teaches sets of nested PCR primers useful for the amplification of nucleic acids of B-MHC (see page 109)".

It is respectfully submitted that the above-rejection does not pertain to the claims as newly amended. Newly amended claim 37 is drawn to at least two oligonucleotides which amplify ß-cardiac myosin heavy-chain DNA. The set of oligonucleotide primers is claimed as being useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being useful in the detection of a hypertrophic cardiomyopathy-associated mutation.

The teachings of Friedman actually teach away from the claimed invention. Friedman studied seven patients with hypertrophic cardiomyopathy and concluded that "mutations in exon 13 of the cardiac B MHC could not be demonstrated in the

myocardium of patients with HCM". Friedman does not teach or suggest a set of oligonucleotide primers useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being useful in the detection of a hypertrophic cardiomyopathy-associated mutation as presently being claimed.

Rejection of Claims 37 and 38 Under 35 U.S.C. § 102(b)

Claims 37 and 38 are rejected under 35 U.S.C. § 102(b) "as being anticipated by Feldman (Circulation (June 1991) 83:1866-1872)". Particularly, the Examiner states that "Feldman teaches compositions comprising sets of nested PCR primers useful for the amplification of nucleic acids of B-MHC (see page 1867)".

It is respectfully submitted that the above-rejection does not pertain to the claims as newly amended. As set forth above, newly amended claim 37 is drawn to at least two oligonucleotides which amplify ß-cardiac myosin heavy-chain DNA. The set of oligonucleotide primers is claimed as being useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being useful in the detection of a hypertrophic cardiomyopathy-associated mutation.

Feldman evaluated gene expression in failing human heart using the polymerase chain reaction. Feldman does not teach or suggest a set of oligonucleotide primers useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being useful in the detection of a hypertrophic cardiomyopathy-associated mutation as presently being claimed

Rejection of Claims 33-35 Under 35 U.S.C. § 103

Claims 33-35 are rejected under 35 U.S.C. § 103 "as being unpatentable over Rosenzweig or Watkins in view of the Stratagene Catalog".

The response set forth above with regard to Rosensweig or Watkins is reiterated here. In brief, the references are the result of the work of the Applicants and therefore are not proper references under 35 U.S.C. §102 (a)/103. The Examiner is respectfully requested to reconsider and withdraw this rejection.

Rejections of Claims 1-12 and 33-35 under 35 U.S.C. § 103

Claims 1-12 and 33-35 are rejected under § 103 as being unpatentable over Geisterfer-Lowrance et al. in view of Mullis (claims 1-7 and 10-12), Almoguera (claims 9 and 10) or Almoguera and further in view of the Stratagene Catalog (claims 33-35). The Examiner contends that it would have been obvious to modify the method of detecting a hypertrophic cardiopathy-associated mutation of Geisterfer-Lowrance et al. by using the teachings of Mullis regarding amplifying nucleic acids or using the RNase protection assay taught by Almoguera. The Stratagene Catalog is being relied upon as "disclos[ing] the general concept of kits for performing nucleic acid detection methods and disclos[ing] that kits provide the advantage of pre-assembling the specific reagents required to perform an assay".

In different embodiments, Applicants' invention pertains to a method for detecting the presence or absence of a mutation associated with hypertrophic cardiomyopathy for facilitating the diagnosis of hypertrophic cardiomyopathy (independent claim 1 and dependent claims 2-12) and kits containing RNA probes and oligonucleotide primers for use in the claimed methods (claims 33-35).

The proper inquiry under section 103 is whether the prior art would have suggested to one having ordinary skill in the art at the time of the invention the claimed method or kit for facilitating the diagnosis of hypertrophic cardiomyopathy and that there was a reasonable expectation of success for the claimed method or kit in view of the prior art. Of the cited references, only the primary reference upon which the rejection is based,

Geisterfer-Lowrance et al., pertains to hypertrophic cardiomyopathy. The secondary references are relied upon for teaching methodologies or the collection of reagents in a kit. Thus, only the Geisterfer-Lowrance et al. reference is pertinent to the issue of whether there is a suggestion of the claimed method or kit in the prior art and a reasonable expectation of success for the claimed method or kit in view of the prior art.

Geisterfer-Lowrance et al. disclose the detection of one point mutation associated with familial hypertrophic cardiomyopathy which occurs in the β cardiac myosin heavy chain gene of affected members of one family with FHC. The β cardiac myosin heavy chain gene mutation results in an Arg403Gln substitution in the β cardiac myosin heavy chain protein. The mutation was detected by the identification of a restriction site polymorphism in the β cardiac myosin heavy chain gene and subsequent sequencing of a subcloned DNA fragment encompassing the mutation.

Geisterfer-Lowrance et al. only demonstrate that afflicted members of a single family with FHC (Family A) have the mutation leading to the Arg403Gln substitution in the β cardiac myosin heavy chain protein. A concurrently published paper (Tanigawa et al.), which is referenced in Geisterfer-Lowrance et al., demonstrates that afflicted members of a different family with FHC (Family B) have a mutation which produces an α/β cardiac myosin heavy-chain hybrid gene. At the time of the present invention, these were the only two families studied with regard to mutations associated with hypertrophic cardiomyopathy and these were the only two disease-associated mutations described in the art. Thus, at the time the invention was made, it was possible that hypertrophic cardiomyopathy in other individuals (i.e., individuals who are not members of Family A or Family B) could be due to 1) a point mutation in amino acid residue 403 of the β cardiac myosin heavy chain protein; 2) an α/β cardiac myosin heavy-chain hybrid gene; or 3) other mutations which had not been described in the art. Geisterfer-Lowrance et al. state (page 1004, lines 37-42):

> Since the cardiac MHC gene mutations that cause FHC have been characterized in only two families, we cannot yet predict whether most affected individuals bear either of these two alleles (indicating that there is a strong founder effect) or whether the disease occurs principally as a result of new mutations.

Therefore, the teachings of Geisterfer-Lowrance et al. would not have suggested to one of ordinary skill in the art at the time of the invention the claimed method for facilitating the diagnosis of hypertrophic cardiomyopathy, since it was unclear from Geisterfer-Lowrance et al. whether mutations in β cardiac myosin heavy chain DNA would be present in subjects having HC who were unrelated to Family A. For example, if HC-associated mutations in individuals unrelated to Family A were in fact α/β cardiac myosin heavy-chain gene fusions (as in Family B) then isolating β cardiac myosin heavy chain RNA from a blood sample from a subject and trying to detect the presence or absence of a hypertrophic cardiomyopathy-associated mutation in the RNA would likely be uninformative.

To reemphasize, prior to the present invention there were no extensive studies involving a large number of families which established that HC could be caused by point mutations in the β cardiac myosin heavy chain gene. Geisterfer-Lowrance et al. do not teach or suggest that a correlation exists between the presence of a mutation in the β cardiac myosin heavy chain gene and the presence of hypertrophic cardiomyopathy in unrelated individuals and thus do not teach or suggest that detection of a mutation in the β cardiac myosin heavy chain gene can be used to facilitate diagnosing the disease in a subject. In contrast, the present invention discloses the study of twenty-five families with members having FHC. Twelve of the twenty-five families displayed point mutations in the β cardiac myosin heavy chain gene. Seven different point mutations, located in four different exons, were detected. (See Example 2, pages 34-38 of the specification). Furthermore, members of Family B (discussed above), who have an α/β cardiac myosin

heavy-chain hybrid gene, were found to also have a point mutation in their other β cardiac myosin heavy chain gene. Applicants have thus discovered that point mutations in the β cardiac myosin heavy chain gene are present in many individuals with hypertrophic cardiopathy from unrelated families (i.e., approximately 50 % of the patients examined) and thus detection of these mutations can be used as an indicator of hypertrophic cardiopathy and for facilitating diagnosis of the disease. It is only based upon this more extensive analysis of individuals with HC that one would be motivated to detect mutations in the β cardiac myosin heavy chain gene in subjects unrelated to Family A as a basis for facilitating the diagnosis of the disease in a subject. Moreover, it is only based upon this more extensive analysis that one would have a reasonable expectation of success in facilitating diagnosis of HC in subjects unrelated to Family A by detecting mutations in the β cardiac myosin heavy chain gene.

The deficiency of Geisterfer-Lowrance et al. in providing the motivation and reasonable expectation of success for the claimed method is not remedied by the teachings of the secondary references which do not pertain to hypertrophic cardiomyopathy. As set forth above, the secondary references are relied upon for teaching methodologies or the collection of reagents in a kit. Thus, only the Geisterfer-Lowrance et al. reference is pertinent to the issue of whether there is a suggestion of the claimed method in the prior art and a reasonable expectation of success for the claimed method in view of the prior art.

SUMMARY

The above rejections either do not pertain to the claims as newly amended and/or are improper and should be withdrawn. The claims are in condition for allowance.

If a telephone conversation with applicant's agent would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' attorney at (617) 227-7400.

Respectfully submitted,

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